

AMENDMENT & RESPONSE UNDER 37 C.F.R. § 1.116 - EXPEDITED PROCEDURE  
Serial Number: 08/565,943  
Filing Date: December 1, 1995  
Title: NON-TOXIC MUTANTS OF PATHOGENIC GRAM-NEGATIVE BACTERIA

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32. [Amended] The method of claim 22 wherein the gram-negative bacterial pathogen is of the genera [Haemophilus, Neisseria, Moraxella, Campylobacter, Shigella or Pseudomonas] *Haemophilus, Neisseria, Moraxella, Campylobacter, Shigella or Pseudomonas*.
33. [Amended] The method of claim 29 wherein the gram-negative bacterial pathogen is of the genera [Haemophilus, Neisseria, Moraxella, Campylobacter, Shigella or Pseudomonas] *Haemophilus, Neisseria, Moraxella, Campylobacter, Shigella or Pseudomonas*.

### REMARKS

#### A. Status of Claims

Reconsideration of this application as amended is requested. Claims 22, 29 and 32-33 having been amended, claims 22-26, 29 and 32-33 are pending. No new subject matter has been added.

The amendments to the claims are fully supported by the specification as originally filed. The amendments are made to clarify the claims, and are not intended to limit the scope of equivalents to which any claim element may be entitled. For example, support for the amendments to claims 22 and 29 regarding the length of the secondary acyl chain is found at page 7, lines 23-26, and at page 13, lines 1-5 of the specification, and in Figures 2A and 2B.

#### B. Rejection of Claims under 35 U.S.C. §112, First Paragraph

Applicant acknowledges that the Examiner has maintained the rejection of claims 22-26 and 29 under 35 U.S.C. § 112, first paragraph and that the rejection will be withdrawn upon the receipt of the required deposit information.

Enclosed herewith is a copy of the deposit receipts and viability statements from the ATCC regarding Nontypeable *Haemophilus influenzae* 2019 B28 and Nontypeable *Haemophilus influenzae* 2019 B29. Also enclosed is a Declaration by Dr. Apicella indicating that the strains described in the specification were deposited under the provisions of the Budapest Treaty, and all restrictions will be irrevocably removed upon the granting of a patent on this application, and the deposits will be replaced if viable samples cannot be dispensed by the depository. The Declaration also states that the strains described in the specification as filed are the same as the

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strains deposited in the depository, and the deposited strains were in Applicants' possession at the time of filing of the above-identified application. Therefore, this rejection under 35 U.S.C. § 112, first paragraph should be withdrawn.

**C. Non-Statutory Double Patenting Rejection**

The Examiner provisionally rejected the pending claims under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 22, 23, 25 and 29 of U.S. Patent Application No. 08/565,943. Applicants will consider filing a terminal disclaimer upon notification of otherwise allowable subject matter. A terminal disclaimer may not be appropriate once the scope of allowable claims is determined in the present application, and dependent upon which application is allowed first.

**D. Objections to the Claims**

Claims 32 and 33 were objected to for minor stylistic reasons. These claims have been amended to overcome these rejections.

**F. Rejections under 35 U.S.C. §103(a)**

The Examiner has rejected claims 22, 23, 25 and 32 under 35 U.S.C. §103(a) as being unpatentable over Karow *et al.*, (*Journal of Bacteriology* 174:7407-7418) in view of Westphal *et al.* (*Methods Carbohydr. Chem.* 5:83-91, 1965). This rejection is respectfully traversed.

The claims as amended recite a method of making a mutant endotoxin that lacks at least one secondary acyl chain on lipid A and that lacks a 3-hydroxy unsaturated C16 fatty acid substitutions on the lipid A as compared to a wild-type bacterial pathogen. This is clearly distinguishable over Karow *et al.*

First, the Karow *et al.* mutant makes a fully hexaacylated lipid A structure. §132 Declaration, ¶ 8 (filed on June 30, 2000). The organism of the present invention contains only lipid A structures that lack at least one secondary acyl chain on lipid A. Second, the Karow *et al.* mutant contains a mixture of new unsaturated fatty acids, most likely palmitoleic (C16:1) in place of the single lauric acid (C12:0) fatty acid. *Id.* The lipid A species of the present invention lacks a 3-hydroxy unsaturated C16 fatty acid substitutions on the lipid A as compared to a wild-

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type bacterial pathogen. Therefore, significant differences exist in the lipid A structures in the *htrB* gene deletion mutants of the present invention as compared to Karow's strain.

Westphal *et al.* does not remedy the deficiencies of Karow *et al.* Westphal *et al.* disclose a method of purifying Gram negative bacterial lipopolysaccharides by phenol-water extraction. They do not, however, teach or suggest a method of making an endotoxin of the present invention, *i.e.*, one that lacks at least one secondary acyl chain on lipid A and that lacks a 3-hydroxy unsaturated C16 fatty acid substitutions on the lipid A as compared to a wild-type bacterial pathogen.

Therefore, the present invention is not obvious over Karow *et al.* in view of Westphal *et al.* and this rejection under 35 U.S.C. §103(a) should be withdrawn.

The Examiner has rejected claims 24, 26, 29 and 33 under 35 U.S.C. §103(a) as being unpatentable over Karow *et al.*, (*Journal of Bacteriology* 174:7407-7418) in view of Westphal *et al.* (*Methods Carbohydr. Chem.* 5:83-91, 1965), and further in view of Gupta *et al.* (*Infect. Immun.* 60: 3201-3208, 1992). This rejection is respectfully traversed.

Karow *et al.* and Westphal *et al.* have been discussed above. Gupta *et al.* does not remedy the deficiencies of Karow *et al.* and Westphal *et al.* Gupta *et al.* disclose the conjugation of chemically-modified LPS to cholera toxin and other proteins. They do not, however, teach or suggest a method of making an endotoxin that lacks at least one secondary acyl chain on lipid A and that lack 3-hydroxy unsaturated C16 fatty acid substitutions on the lipid A as compared to a wild-type bacterial pathogen.

Therefore, the present invention is not obvious over Karow *et al.* in view of Gupta *et al.* and this rejection under 35 U.S.C. §103(a) should be withdrawn.

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### CONCLUSION

Applicant believes that all claims are in condition for allowance. Reconsideration of the rejections of the claims and allowance of all the claims is respectfully requested. The Examiner is invited to contact the Applicant's attorney if prosecution of the present application can be assisted thereby.

Respectfully submitted,

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By their Representatives,

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Date 8 December 2000

By

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**Date:** November 17, 2000

**To:** Ann S. Viksnins  
**Fax Number:** 612 339-3061

**From:** ATCC Patent Depository **Number of pages:** 1 (Including this page)


**REFERENCE:** Patent Deposit (Ref: Docket or Case No. 875.001US2-UIRF N5-50)

Nontypeable Haemophilus influenzae: 2019 B28 assigned PTA-2667 and  
Nontypeable Haemophilus influenzae: 2019 B29 assigned PTA-2668

Date of Deposit: November 14, 2000. Paperwork will be forwarded to you in a few days. An invoice will be sent under separate cover referencing the VISA account of Suzanne Hoofnagle:

Standard storage/informing	\$ 2,200.00
Viability Test	<u>300.00</u>

Total amount to PTA-2667 and PTA-2668 \$ 2,500.00

  
\_\_\_\_\_  
Marie Harris, Patent Specialist  
ATCC Patent Depository

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